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(71) Déposant *(pour tous les Etats désignés sauf US)*: LABORATOIRE L. LAFON [FR/FR]; 19, avenue du Professeur-Cadiot, F-94701 Maisons-Alfort Cédex (FR).

(72) Inventeurs; et
(75) Inventeurs/Déposants *(US seulement)*: NGUYEN, Thanh-Tam [FR/FR]; 27, avenue Alsace-Lorraine, F-94450 Limeil-Brevannes (FR). JACQUOT-LEYDER, Joëlle [FR/FR]; 7, rue du Cap, F-94000 Créteil (FR).

(74) Mandataire: CLISCI, Serge; S.A. Fedit-Loriot et Autres, Conseils en Propriété Industrielle, 38, avenue Hoche, F-75008 Paris (FR).

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(54) Title: EXTRUSION AND FREEZE-DRYING METHOD FOR PREPARING PARTICLES CONTAINING AN ACTIVE INGREDIENT

(54) Titre: PROCEDE DE PREPARATION DE PARTICULES RENFERMANT UN INGREDIENT ACTIF PAR EXTRUSION ET LYOPHILISATION

(57) Abstract

A method for preparing particles each of which consists of a carrier forming a matrix, and at least one active ingredient uniformly distributed throughout said matrix. The method comprises extrusion and freeze-drying steps, wherein 1) (a) at least one active ingredient, (b) a physiologically acceptable hydrophilic carrier, and (c) water are uniformly mixed to give a pasty mixture with a viscosity at room temperature (15-20 °C) of under 1 Pa.s; 2) the resulting uniform mixture is extruded and the extrudate is broken up into moist particles; 3) the resulting particles are frozen as they fall under their own weight into an inert gas stream at a below-zero temperature; and 4) said particles are freeze-dried.

(57) Abrégé

La présente invention concerne un procédé pour la préparation de particules comprenant chacune un excipient formant une matrice et au moins un ingrédient actif régulièrement réparti dans la masse de ladite matrice, ledit procédé, qui comprend les opérations d'extrusion puis de lyophilisation, étant caractérisé en ce qu'il comprend les étapes consistant dans: 1) la préparation d'un mélange homogène à partir (a) d'au moins un ingrédient actif, (b) d'un excipient hydrophile physiologiquement acceptable, et (c) d'eau, de façon à obtenir un mélange pâteux ayant une viscosité, mesurée à la température ambiante (15-20 °C), inférieure à 1 Pa.s; 2) l'extrusion du mélange homogène, ainsi obtenu, et la découpe de l'extrudat pour obtenir des corpuscules humides; 3) la congélation desdits corpuscules, ainsi obtenus pendant qu'ils tombent par gravité dans un courant gazeux inerte ayant une température inférieure à 0 °C; et 4) la cryodessiccation desdits corpuscules.

English translation of French language PCT publication

METHOD FOR THE PREPARATION OF PARTICLES CONTAINING AN ACTIVE INGREDIENT BY EXTRUSION AND LYOPHILIZATION

The present invention is concerned with a new process for the preparation of isolated particles, each of which contains at least one active ingredient useful in therapeutics, cosmetics, dietetics or alimentation, by extrusion and then lyophilization.

It is also concerned with the said particles as new industrial products, constituted by an intimate combination of a physiologically acceptable excipient and at least one active ingredient, and obtained according to the said process by extrusion and then lyophilization.

These particles, which will be called below "microparticles" and which have a maximum dimension between 0.05 mm and 5 mm, are essentially obtained in the form of little rods, or better still, in the form of spheres (also called "microspheres", "pearls", "beads" or "microbeads").

PRIOR ART

It is known that microparticles have already been obtained for therapeutic or alimentary usage by (i) extrusion, at a temperature which is in general greater than or equal to 45°C, of an intimate mixture of an active ingredient and of a fusible physiologically acceptable excipient, through an extrusion head having one or several dies, (ii) cutting the resulting extrudate at the level of each die, notably with the aid of a plate or with periodic vibrations and (iii) drying the resulting particles by generally allowing them to fall by gravity using an ascending inert gas (i.e., circulating countercurrent to the path of the particles). See in this connection the published European Patent Application EP-A-0204596, which describes the preparation of cylindrical rods (see column 4, lines 52-57), on the one hand, and the published European Patent Application EP-A-0438359 and the published German Patent Application DE-B-2 725 924 ("Auslegeschrift"), which describe the preparation of spherical microparticles by extrusion under vibrations (specifically at a frequency of 200-400 Hz or 1800-2500 Hz according to DE-B-2 725 924), on the other hand. Other modes of the extrusion technique appear in granted US Patent US-A-2 918 411 and in published European Patent Application EP-A-0465338.

According to the prior art cited above, the excipient comprises or essentially consists of a lipid material, preferably one which is not soluble in water, can be melted and which acts as a solvent for the active ingredient. This lipid material is needed to obtain microparticles of a regular shape, notably as microbeads, which neither adhere nor agglomerate to one another during solidification. According to the said prior art, the said lipid material is heated to melt it, and then the active ingredient is introduced into the resulting molten mass and, optionally, other components of the physiologically acceptable excipient are added to form a mixture which has a sufficient viscosity [less than 60 cP (i.e. 0.06 Pa·s) and preferably between 10 and 20 cP (i.e. 0.01 and 0.02 Pa·s); according to the information furnished in DE-B-2 725 924, column 3, lines 52-57] at the temperature of the extrusion head; and, then, the extrudate is cut (at the exit from the extrusion head) with the aid of a plate or knife (to obtain rods) or with the aid of periodic vibrations (to obtain microspheres) to form droplets which are generally solidified with the aid of an inert gas flowing countercurrent while the particles fall by gravity.

In particular, EP-A-0 438 359 recalls (see page 2, lines 25-29) that the utilization of a very cold countercurrent or gaseous jet (-10°C to -20°C) against the microparticle current, has the disadvantage of increasing the viscosity of the product that one wishes to solidify and consequently slows down the crystallization of the active ingredient. Also, EP-A-0 438 359 recommends the use of cooling, which is not that intense (see page 2, lines 30-31) and the use of fluidized bed at the receptacle of the microparticles to maintain the microspheres which have not yet been completely solidified in the fluidized state.

It should also be pointed out that US-A-2 918 411 provides for the solidification of the molten mass at ambient temperature (this patent uses the expression "congealed mass", column 2, line 28 or "congealed" as the meaning of "solidified" as it follows from the mode of operation given in Example 1; in this regard, see column 3, lines 67-68, where the following expression appears: "the congealed mass is cooled to room temperature").

The use of a pasty mass containing water goes manifestly against the information of prior art relating to extrusion technique illustrated by documents DE-B-2 725 924, US-A-2 918 411, EP-A00 438 359, EP-A-0 465 338 and EP-A-0 204 596.

It is known that lyophilization is a particular case of cryodesiccation when the solvent of a material that one wishes to eliminate is water. Lyophilization includes a phase called solidification and then a phase called sublimation, during which the water, that one wishes to eliminate, is eliminated by reheating under reduced pressure. The technique of lyophilization is well-known and can be specifically illustrated by patents EP-B-0 159 237, US-A-4 178 695, US-A-4 490 407 and US-A-4 883 507.

Patents US-A-4 490 407 and US-A-4 883 507 described in particular the preparation of spherical, coated microparticles having a diameter within the range of 10-120 μm (according to US-A-4 490 407) or preferably less than 1 μm (according to US-A-4 883 507), by spraying, drying with the aid of a gaseous current and then (a) lyophilization in the alveoles of an aqueous composition containing the said coated microparticles (see US-A-4 490 407, column 3, lines 1-3 and column 4, lines 32-33) or (b) collecting on a filter

consisting of a porous mass with gas and obtained by congelation, grinding, sublimation of the solvent and compression (see US-A-4 883 507 in column 10, line 30 to column 11, line 26).

Moreover, it is known that lyophilization has some advantages. It permits conservation of the initial characteristics of the active ingredients, or those that were produced during their manufacture on the one hand, and to protect the active ingredients from alterations due to heat and water (notably by avoiding hydrolysis and oxidation reactions), on the other hand.

During storage, it improves the stability of the active ingredients, specifically at two levels:

- the chemical stability, which avoids alteration of the molecules present in the form of fine active particles, and
- the physical stability which avoids denaturation of the characteristics of the form obtained, the said denaturation involving slowing down of the liberation of the active ingredient, and a modification of the organoleptic properties (such as consistency of taste), such a disadvantage being harmful with regard to the observance (i.e. following and observation of the prescribed posology) and consequently, the efficacy of the active ingredient.

Lyophilization also permits one to avoid physical transformations of the dry products after the removal of the solvent (in this case, water), such as recrystallization and polymorphism as is frequently the case during liquid/vapor evaporation by heat on the one hand and to obtain, starting from substances which dissolve slowly, preparations which are more easily soluble in water, on the other hand. Thus, during the sublimation phase, which takes place during lyophilization in order to eliminate the water, the dissolved molecules do not agglomerate to form crystals, as is the case during evaporation, and the dry product obtained theoretically remains as divided as it was in the initial solution.

Moreover, lyophilization permits combination of substances which are physicochemically incompatible in solution. From this point of view, it permits the replacement of effervescent compositions, notably effervescent tablets by lyophilizates.

Finally, lyophilization contributes to the surface treatment of particles to increase their hydrophilic nature. Thus, oral lyophilizates based on active ingredients, which are normally insoluble or sparingly soluble in water, give a suspension in water in which they are found in the state conferred initially after a treatment, such as micronization, dispersion, surface treatment, etc. Moreover, the porous structure of the lyophilizates prevents agglomeration of the particles during dispersion of the said lyophilizates in water: the integrity of the initial particle size distribution is retained and particularly bothersome electrostatic phenomena are eliminated.

PURPOSE OF THE INVENTION

There is a need to improve the bioavailability of active ingredients which are packaged in the regular geometric form of the matrix type of a physiologically acceptable excipient, which contains the said active ingredients in its bulk and which is obtained by extrusion.

There is also a need to provide matrix particles of the type cited above, which have the advantages of lyophilizates.

Thus, according to the invention, it is proposed to furnish a new technical solution using extrusion and lyophilization to satisfy the needs cited above and to obtain particles with a regular geometric shape that have the advantages provided by lyophilization. This novel technical solution, which comprises extrusion of a pasty mixture containing water, goes against the information contained in the prior art with regard to the manner of extrusion, according to which one would have to (i) avoid the presence of water in the material that one wishes to extrude and (ii) would have to use consequently a meltable lipid material in which the active ingredient was solubilized, in order to obtain particles of regular geometric shape after solidification.

According to a first aspect of the invention, it is proposed to furnish a method for the preparation of isolated and geometrically regular particles, each matrix-type excipient containing in its bulk at least one active ingredient, the said method avoiding agglomeration of the said particles among themselves or to the wall of their container during their formation.

According to a second aspect of the invention, it is proposed to furnish particles obtained according to this method, namely, by extrusion of a pasty mixture containing water, followed by lyophilization, each of the said particles containing at least one therapeutically, cosmetically, dietetically or nutritionally active ingredient which is useful for humans or animals.

According to a third aspect of the invention, it is proposed to furnish a method of packaging according to which one coats each of the said particles with a polymer coating having a continuous wall. The technique of coating used according to the invention, as it will be seen later, is different from that of coating of tablets, which is not applicable here considering the dimensions and especially the porosity of the lyophilizate.

OBJECTIVE OF THE INVENTION

The goal of the invention is reached with the aid of a new technical solution for the preparation of matrix particles by extrusion or forming followed by lyophilization.

According to the invention, a method is recommended for the preparation of particles which are useful, notably in therapeutics, each particle comprising an excipient that forms a matrix and at least one active ingredient uniformly distributed in the bulk of the matrix, the said method being characterized by the fact that it includes the production of dry cores of regular shape, preferably spherical shape, by extrusion or forming, followed by lyophilization, each dry core being then being suitable to be coated on the one hand or suitable to be involved in a more complex operation, on the other hand.

According to a variation of the embodiments, this method comprises more particularly

- the preparation of a pasty mixture having a viscosity less than 1 Pa·s, measured at ambient temperature (15-20°C),
- extrusion of the said pasty mixture and cutting of the extrudate, as obtained, in the form of wet particles with a size generally between 0.01 and 5 mm,
- solidification of the said particles by contact with an inert fluid at a temperature below 0°C, and then
- drying the said particles thus solidified by cryodesiccation.

The solidification is carried out while the wet particles are dropping in a gaseous cooled fluid that preferably circulates countercurrent.

According to the invention, the particles are recommended as industrial product, optionally coated, inside of a polymer membrane with continuous wall, obtained according to the said method and having a maximum dimension between 0.05 and 5 mm.

BRIEF DESCRIPTION OF THE DRAWINGS

The drawings attached in the Appendix do not represent a limitation but illustrate other advantages and characteristics of the invention.

More precisely:

- Figure 1 represents schematically an installation that permits carrying out the method of preparation of the invention on an industrial scale;
- Figure 2 represents in the form of a diagram an embodiment of the method of the invention; and
- Figure 3 represents schematically a particle according to the invention (here a microbead) obtained by extrusion, lyophilization and then coating.

DETAILED DESCRIPTION OF THE INVENTION

The method according to the invention permits one to obtain particles (called "microparticles" here) of a regular geometrical shape, of the matrix type excipient containing at least one active ingredient in its bulk.

The method according to the invention for the preparation of particles having at least one excipient forming a matrix and at least one active ingredient uniformly distributed in the bulk of the said matrix, the said process comprising the operations of extrusion and then lyophilization, is characterized by the fact that it includes the steps consisting of:

(1) preparation of a homogeneous mixture from

- (a) at least one active ingredient,
- (b) a hydrophilic physiologically acceptable excipient, and
- (c) water,

so as to obtain a pasty mixture which has a viscosity less than 1 Pa·s, measured at ambient temperature (15-20°C);

(2) the extrusion of the homogeneous mixture thus obtained and the cutting of the extrudate to obtain wet particles;

(3) solidification of the said particles thus obtained, while they fall by gravity in an inert gaseous current having a temperature less than 0°C; and,

(4) drying of the said particles by cryodesiccation.

Optionally, the method according to the invention comprises another step consisting of:

(5) coating each of the lyophilized particles (i.e., the particles dried by cryodesiccation) inside a polymer membrane with continuous wall.

During the formation of the microparticles, the extrudate (called "parison" by the expert in the field) is fragmented mechanically at the exit of the extrusion head, which may have one or several dies. The fragmentation can be carried out with the aid of a rotating cutter or with a pivoting plate going back and forth, obtaining little, essentially cylindrical, rods; it can also be carried out with the aid of vibrations, in order to obtain microbeads which are essentially spherical.

According to a variation, little cylindrical rods are obtained which, as in the prior art, have a length of 1 to 5 mm and a diameter from 1 to 1.5 mm, from circular dies, on the one hand, and approximately cylindrical or oblong little rods, notably with a length of 1 to 5 mm and a thickness of 1 to 1.5 mm, from elongated dies, on the other hand. The fragmentation or cutting in this case is done with the aid of a cutter or a blade, cutting at the said dies, according to the periodicity. If one uses elongated dies, it is possible to provide one or several weakened areas in the material on at least one surface of the rods in order to obtain scored products.

According to another variation, the microbeads are obtained by periodic vibrations or oscillations of the extrusion head or of its die or dies. These periodic vibrations or oscillations have a frequency notably comprised between 50 Hz and 10,000 Hz, or even higher than 10,000 Hz; they permit breaking up the flux of extrudate, leaving the extrusion head producing identical volumes, producing microbeads having a final calibrated diameter (i.e. after lyophilization) between 0.1 and 3 mm and preferably between 0.1 and 1.8 mm.

Since, according to the invention, microbeads rather than little rods are preferred, the description which follows is concerned essentially with the production of microbeads unless otherwise indicated, but the information relating to the said microbeads can be directly transposed to little rods.

In step (1), the expression "substantially hydrophilic excipient" means that the hydrophilic excipient is present in the homogeneous mixture in the extruder in a quantity greater than or equal to 5% by weight with respect to the weight of the said mixture,

the entire hydrophilic excipient/water representing a quantity greater than or equal to 15% by weight with respect to the said mixture. In other words, the excipient that forms the matrix of the microbeads consists either completely of a hydrophilic excipient (general case) or comprises a combination of a lipophilic excipient and a hydrophilic excipient (special case of a matrix made from an oil-in-water suspension).

The hydrophilic excipient (b) has two essential components:

(b1) a polymer component having a molecular weight greater than or equal to 10,000 daltons, swelling in the presence of water, and

(b2) a water-soluble or water-dispersible component that serves as diluent.

Component (b1) is involved as binder in the formation of microparticles or microbeads, on the one hand, and as an agent that facilitates the disintegration of the said microparticles or microbeads after lyophilization at the time of their utilization, upon contact with water or an aqueous medium, on the other hand.

Practically speaking, the said component (b1) will be a substance with a high molecular weight, notably, above 10,000 daltons, and belongs to the group of colloids or polymers which can swell in the presence of water, on the one hand, and their mixtures, on the other hand. Advantageously, the said component (b1) will be a substance chosen from the group constituted by gum arabic, xanthan gum, tragacanth gum, alginates, pectinates, polyvinylpyrrolidone, polyethylene glycols, cellulose, carboxymethylcellulose, cellulose ethers, carboxymethylchitin, dextran, chitosan (which is obtained by total or partial deacetylation of chitin), gelatin, acrylic and methacrylic polymers and copolymers, colloidal silica and their mixtures.

Preferably, a component (b1) will be chosen from the group constituted by gum arabic, xanthan gum, polyvinylpyrrolidone, carboxymethylcellulose, cellulose ethers (notably methyl-, ethyl-, propyl-, hydroxyethyl- or hydroxypropylcellulose), dextran and their mixtures.

Advantageously, it is recommended to use 10 to 350 parts by weight of component (b1) per 100 parts by weight of active ingredient.

The component (b2) is used as physiologically inert diluent (or ballast) of the active ingredient and serves to provide cohesion of the microparticles or microbeads during formation and during their storage before utilization. In other words, it contributes to giving "body" to the said microparticles or microbeads, since the content of active ingredient present in the final lyophilized material may be low. With regard to its water-soluble or water-dispersible nature, component (b2) has a favorable action on the disintegration of the said lyophilized microparticles or microbeads. Advantageously, the said component (b2) will be a substance chosen from the group consisting of sugars, dextrans and their mixtures.

Preferably, a component (b2) will be used, chosen from the group consisting of lactose, glycine, mannitol, glucose, sucrose, maltodextrin, cyclodextrin and its derivatives, synthetic sweeteners (notably aspartame and other analogous dipeptides, cyclamates and saccharinates), natural or synthetic aromas, and their mixtures.

"Cyclodextrin" is defined here as any compound of the cycloamylose type [see Merck Index, (1989), 11th edition, page 425, entry "Cyclodextrins" (No. 2724)], in particular, α-cyclodextrin or cyclohexaamylose having the molecular formula $C_{36}H_{60}O_{30}$, ß-cyclodextrin or cycloheptaamylose having the molecular formula $C_{42}H_{70}O_{35}$, and γ-cyclodextrin or cyclooctaamylose having the molecular formula $C_{48}H_{80}O_{40}$.

"Cyclodextrin derivatives" is defined here as any cyclodextrin compound in which at least one of the OH groups is etherified or esterified. Notably, the said cyclodextrin derivatives include ethers in which the hydrogen atom of at least one OH group is replaced by a C_1-C_4 alkyl group or by a C_1-C_4 hydroxyalkyl group, that is, in particular, hydroxyethylcyclodextrins, hydroxypropylcyclodextrins and dimethylcyclodextrins.

Advantageously, it is recommended to use 5 to 350 parts by weight of component (b2) per 100 parts by weight of the active ingredient.

Optionally, the hydrophilic excipient according to the invention may contain a third component (b3), which is a surfactant with a hydrophilic character. Among suitable surfactant compounds, one can cite notably classical galenic surfactants that can be administered orally, in particular, polysorbates, sorbitan esters, polyethers of fatty glycerides, lecithins, sodium lauryl sulfate, sodium dioctylsulfosuccinate and their mixtures.

The quantity of surfactant component (b3) to be used in step (1) is not critical. When the said component (b3) is introduced into the pasty mixture to be extruded, this being mainly the case of a mixture containing an active ingredient which is not water-soluble or water-dispersible, it will be used generally in a quantity of 0.05 to 3 parts by weight per 100 parts by weight of the active ingredient.

The active ingredient which is used in step (1) can be liquid or powder, and it can be either soluble in water or insoluble in water. When it is in the powder form, its particle size range will be between 1 and 1000 μm. Since a very large particle size range (for example, greater than or equal to 500 μm) does not permit one to obtain lyophilized microparticles or microbeads with a very low size according to the invention, when the active ingredient is insoluble in water, it is recommended to use powders of the active ingredient which have a particle size range between 1 and 200 μm. One obtains powders with a particle size range of 1 to 30 μm by micronization with a jet of air and a particle size range from 30 to 200 μm by grinding. When the powdered active ingredient is not soluble in water, it will be incorporated into the mixture before being extruded, so as to obtain an emulsion, notably of the oil-in-water type, the said ingredient being then incorporated in the aqueous phase or in the oily phase during the preparation of the said mixture.

Water is added in step (1) to permit subsequent lyophilization on the one hand and, above all, to adjust the viscosity of the pasty mixture, on the other hand. According to a characteristic of the invention, it is essential that the pasty mixture that is subjected to extrusion have a viscosity less than 1 Pa·s. From the practical point of view, it is recommended that the said mixture, which will be extruded, have a viscosity between 0.1 and 0.3 Pa·s at ambient temperature, that is, a viscosity different from that recommended in DE-B-2 725 924 (that is, 0.01-0.02 Pa·s, as recalled above).

It is important that the said pasty mixture, which contains water and which will be extruded, be homogeneous; if necessary, after it is formed, when such a mixture is insufficiently homogeneous, it can be "smoothened" by passage through a homogenizing device.

The extrusion of step (2) is carried out at ambient temperature, as indicated above. In other words, in order to have such a temperature, the temperature of the extrusion head will be controlled at 15 to 20°C. This extrusion consists in forcing the passage of the pasty mixture through an extrusion head which has one or several dies of a given diameter, the said extrusion head being subjected to periodic vibrations or oscillations to form spherical droplets.

According to another characteristic of the invention, it is important to solidify the droplets relatively rapidly to "fix" them in the form which they have after fragmentation or cutting (here by vibrations) at the exit of the extrusion head. Thus, the solidification of step (3) is carried out with the aid of an inert gas current (notably nitrogen or argon) having a temperature less than 0°C and preferably less than -10°C. The droplets formed by gravity (or by excess pressure, which is the same thing) while the gaseous solidifying current goes (preferably) countercurrent to the flux (or trajectory) of the said droplets.

The solidification of step (3) with the aid of an inert gas current constitutes either the beginning of the solidification phase of the lyophilization process or the totality of the said phase.

The solidification phase of lyophilization comprises cooling of the mass to be lyophilized to a temperature between -18 and -80°C, preferably to a temperature from -30 to -50°C. Thus, for example, the inert gas current initiates the solidification by cooling the droplets to -12°C, and then complete solidification occurs in the lyophilizer until a temperature less than or equal to -18°C is reached (or less than or equal to -30°C, as indicated above). On the other hand, if the inert gaseous current cools the said droplets to a temperature of -45°C for example, then solidification in the lyophilizer does not have to be performed.

In step (4), the phase of sublimation of water in the lyophilization technique is carried out in the classical manner, with a temperature gradient and a reduced pressure gradient (i) to go from the solidification temperature at 1 bar to a temperature of 25-40°C at 0.3 mbar (in 1 to 2 hours) and then (ii), to continue sublimation for 10 minutes at 25-40°C at 0.05 mbar.

Advantageously, the lyophilization is performed using plates lined with a monolayer of solidified droplets.

The installation of Figure 1, for carrying out the method of the invention, comprises, schematically, a mixer 100 equipped with a rotating agitator 101, where the mixture is prepared of component (a), the active ingredient, of the components of the excipient, including components (b1), (b2) and optionally (b3), and of component (c), water. After homogenization, the active ingredient is present in this mixture in the form of a solution, suspension of emulsion.

With the aid of a device 102, mixer 100 feeds a container 103, in which a vibration device with periodic oscillation 105 connected to the extrusion head is arranged. These vibrations are produced by a frequency generator 104.

From a die 112, the droplets (not shown) fall by gravity toward the bottom of container 103 to form ensemble 106. Under the action of a cold inert gas flow (not shown) which is ascending (i.e. circulating countercurrent with respect to the flux of the droplets), the said droplets are solidified (for example, at -15°C). With the aid of a device 107, the solidified droplets are charged onto a lyophilization plate 108 and then introduced into lyophilizer 109 which comprises notably a tunnel 110 and a cooling device 111 (end of the said solidification phase of -18 to -80°C) and heating (sublimation phase).

Moreover, orifices (not shown) are provided for the removal of the cooling gas flow at the top of container 103 and/or laterally at the level of the extrusion head or slightly below.

If necessary, the portion of container 103 that contains the ensemble of solidified droplets 106, device 107 and plate 108 can be located inside a cooling container (not shown).

Optionally, if necessary, to avoid disintegration of the droplets on the one hand and their agglomeration (among themselves or to the wall), on the other hand, the contents of the assembly of elements 106, 107 and 108 or at least one of these (notably 106 and 108) can be placed into a fluidized bed. Such a fluidized bed is advantageous for obtaining, in particular, filling of the plate 108 in the form of a monolayer of solidified droplets.

Figure 2 is a diagram illustrating an embodiment of the method of the invention for the preparation of microbeads. This diagram includes:

- at 200, the preparation of the mixture containing the active ingredient (a), the hydrophilic components (b1), (b2) and optionally (b3), which is the physiologically acceptable excipient, and water; this mixture has a viscosity between 0.1 and 0.3 Pa·s;
- at 201, the extrusion of this mixture under vibration to obtain droplets;
- at 202, isolated droplets 10 falling by gravity;
- at 203, the solidification of the droplets 10 by means of a countercurrent inert gas flow, in order to obtain isolated and solidified droplets 11;
- at 204, the lyophilization of the isolated and solidified droplets 11, to obtain lyophilized microbeads 1; this lyophilization includes the continuation of solidification and then sublimation of the water;
- the lyophilized microbeads 1 obtained at 204 are then either (i) packaged at 205 into bottles, or (ii) are coated at 206 with a polymer coat 2 with a continuous wall and preferably a porous one and then are directed according to arrow 207 toward packaging, notably into bottles as at 205.

At step (5), coating of the isolated microbeads is performed, if this is preferable, these microbeads having been obtained according to the method of the invention by extrusion and then lyophilization. As indicated above, the coating of the lyophilizate, as it is done for tablets, cannot be realized, even if one knows that one can incorporate coated products into oral lyophilizates. On the other hand, it is entirely possible to coat the microbeads, notably, in order to mask the taste of bitter and unpleasant products, to prolong or modify the

liberation of the active ingredient or to protect active ingredients that are sensitive to external degradation agents.

The lyophilized microbeads can be coated with various gastric-juice soluble agents, either in an organic medium or in an aqueous medium, after prior isolation. The coating can be done by spraying in a bed fluidized with air, notably of the GLATT or WÜRSTER type.

Among the coating agents, one can cite specifically:

- semisynthetic cellulose derivatives, such as, specifically, methylcellulose, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose phthalate and cellulose phthalate/acetate,
- esters of polyacrylic acid and polymethacrylic acid,
- copolymers of ethylene/vinyl acetate,
- polymethylsiloxanes,
- polyacrylamides,
- polyvinylpyrrolidones and poly(vinyl acetate),
- polylactic, polyglycolic acids and their copolymers,
- polyurethane,
- polypeptides,
- etc.

Coating of a lyophilized microbead with a microporous, semipermeable membrane, obtained by incorporation of soluble products in the polymer film, with a continuous wall, leads to the formation of a type of elemental osmotic pump without supplemental addition of an osmotic agent such as sodium and potassium salt; since, by definition, the lyophilized product is very hydrophilic, it has a tendency to absorb water from the exterior when it is placed in the presence of water; the water dissolves the active ingredient and it creates an osmotic pressure which expels the aqueous solution containing the active ingredient.

The product dissolved with water leaves the microbead gradually as water penetrates into it. Thus, one obtains regular liberation of the active substance. By using an appropriate formulation of the oral lyophilizate and with judicious choice of the membrane, one can

modulate the liberation of active ingredients "upon demand", which permits efficient chronotherapy.

Figure 3 illustrates schematically the operation of the lyophilized and coated micro-beads as osmotic "pumps" or "reservoirs". Microbead 1, which contains here an active ingredient in the form of microparticles 3, is coated with a semipermeable coating or envelope 2. After oral administration, the water or aqueous body fluids (in the case in question, gastric juice), penetrates envelope 2 along arrows 4 and then leaves from it along arrows 5 while entraining the active ingredient 3 along arrows 6. This mode of operation is suitable when the active ingredient is soluble in water and the body fluids contain water.

As a variation, one can provide gastric-juice-resistant coating in order to liberate the active ingredient in the enteral area.

BETTER EMBODIMENT

A better embodiment of carrying out the method according to the invention consists in preparing microbeads having a diameter calibrated in the range of 0.1-1.8 mm, by proceeding as follows:

(1) preparation (at ambient temperature) of a homogeneous mixture having a viscosity between 0.1 and 0.3 Pa·s from

(a) 100 parts by weight of an active ingredient,

(b) a substantially hydrophilic excipient containing

(b1) 10 to 350 parts by weight of a polymer component having a molecular weight greater than or equal to 10,000 daltons, which swells in water and chosen from the group consisting of gum arabic, xanthan gum, polyvinylpyrrolidone, carboxymethylcellulose, cellulose ethers (specifically, methyl-, ethyl-, propyl-, hydroxyethyl- or hydroxypropylcellulose), dextran and their mixtures,

(b2) 5 to 350 parts by weight of a water-soluble or water-dispersible component serving as diluent and chosen from the group consisting of lactose, glycine, mannitol, glucose, sucrose, maltodextrin, cyclodextrin and its derivatives, synthetic sweeteners (specifically, aspartame and other analogous dipeptides, cyclamates and saccharinates), natural or synthetic aromas and their mixtures, and

(b3) optionally, 0.005 to 3 parts by weight of a surfactant component, and

(c) water in a quantity sufficient for obtaining the said viscosity of 0.1-0.3 Pa·s;

(2) extrusion of the mixture thus obtained at ambient temperature (15°C to 20°C) and fragmentation of the extrudate with the aid of vibrations at a frequency of 50 to 10,000 Hz (these vibrations being applied specifically to the extrusion head);

(3) solidification of the droplets thus obtained, with the aid of a countercurrent inert gas flow, while the said droplets are falling by gravity, the solidification being continued in a lyophilizer to a temperature of -30°C to -50°C, and

(4) elimination of the water in the said lyophilizer by sublimation.

According to this better embodiment, the collection of the solidified droplets by the countercurrent is made in the form of a monolayer, and the lyophilization is also carried out in the form of a charge of droplets also constituting a monolayer.

Regarding the utilization of the lyophilized microparticles of the invention, it should be pointed out that

- in human and veterinary therapy, notably for warm-blooded animals, such as mammals, microbeads, optionally coated (having a diameter calibrated between 0.1 and 1.8 mm) are recommended, destined to be administered orally;
- in cosmetics, coated microbeads are recommended (having a calibrated diameter between 0.05 and 0.5 mm) destined to be incorporated in cream-type, ointment or lotion preparations; the coating of the said microbeads may contain collagen (or modified collagen) which is cleavable by collagenases contained in perspiration;
- in human dietetics, microbeads or small rods are recommended; and
- in the field of foods, both for humans and animals, little rods are recommended, containing an antibiotic, a growth factor, an amino acid, a peptide or one of their mixtures as active ingredient.

Other advantages and characteristics of the invention will be understood better upon reading the practical examples which follow, which, nevertheless, do not represent a limitation but are given by way of illustration.

EXAMPLE 1 **Paracetamol microbeads**

A mixture to be extruded is prepared, having the following formulation:

Paracetamol	100.00 g
Dextran 70,000	10.00 g
Xanthan gum	0.05 g
Lactose	15.00 g
Polysorbate 60	0.40 g
Water	120.00 g

The lactose, polysorbate 60 and dextran 70,000 are dissolved in the water. Then the paracetamol (grain size 50-200 μm) is added, dispersed with the aid of a homogenizer operating at an angular velocity of 2000 rpm for 2 minutes. Thus a mixture is obtained which has a viscosity between 0.1 and 0.3 Pa·s at ambient temperature.

This mixture is introduced into an extruder, the extrusion head of which has several dies, each having an orifice with a diameter of 0.5 mm and each subjected to vibrations at a frequency of 100 Hz. The droplets formed are solidified with the aid of a countercurrent flow of nitrogen and then brought in the form of a monolayer (during the solidification phase of the lyophilizer) at a temperature between -40°C and -45°C.

The water in the solidified droplets is eliminated by sublimation by reheating to +35°C at a pressure of 0.300 mbar and then, for 10 minutes at +35°C, to a pressure of 0.050 mbar.

The lyophilized microbeads thus obtained have an excellent mechanical strength and have a particle size of 1.200 mm.

EXAMPLE 2 **Microbeads of probucol**

Starting from a mixture having the following formulation:

Probucol	100 g
Sodium lauryl sulfate	2 g
Dextran 70	13 g
Lactose	30 g
Water	300 g

on prepares microbeads in the manner described in Example 1, with the difference that the particle size of Probucol is 2 to 10 μm and the dies have a diameter of 0.6 mm. Thus, lyophilized microbeads are obtained with a diameter of 1.5 mm.

EXAMPLE 3 **Microbeads of piroxicam**

Starting from a mixture having the following formulation:

Piroxicam	2.00 g
Dextran 70	6.00 g
Xanthan gum	0.05 g
Lactose	6.00 g
Tween 60	0.10 g
Water	500.00 g

microbeads are prepared using the mode of operation described in Example 1, with the difference that the particle size of piroxicam is 2 to 5 μm and that the dies have a diameter of 0.2 mm. One obtains lyophilized microbeads which have a diameter of 0.500 mm.

EXAMPLE 4 **Microbeads of phloroglucinol**

Starting from a mixture having the following formulation:

Phloroglucinol	80 g
Dextran 70	20 g
Aspartame	2 g
Mannitol	10 g
Water	500 g

lyophilized microbeads are prepared according to the method of operation of Example 3, their diameter being 0.500 mm.

EXAMPLE 5 **Tiadenol microbeads**

Starting from a mixture having the following formulation:

Phase A:	
Tiadenol	100 g
Polysorbate 60	2 g
Fatty acid polyethoxy ether	2 g
Miglyol 812	20 g
Phase B:	
Dextran 70	10 g
Lactose	5 g
Water	50 g

microbeads are prepared according to the protocol which includes the preparation of the mixture of Phase A at 70°C and that of Phase B at 70°C, mixing of A and B, homogenizing the resulting mixture using a Turrax-type apparatus, operating at an angular velocity of 5000 rpm for 5 minutes, introduction of the resulting homogeneous mixture into the extruder and

then reproducing the method of operation described in Example 2. The lyophilized microbeads obtained have a particle size of 1.5 mm.

EXAMPLE 6 **Coating**

The microbeads obtained in Example 1 were coated to mask their aftertaste, using the following coating solution:

Ethylcellulose	12.5% by weight
Lactose	10% by weight
Dibutyl phthalate	1% by weight
Isopropanol	66.5% by weight

Into an apparatus with a bed fluidized with air of the type GLATT WSG 5, 1 kg of microbeads are introduced and the apparatus is heated to 50 to 55°C so as to have the temperature of the coated product as 30-35°C. The coating solution described above is sprayed at a flow rate of 2-4 mg/min and a spraying pressure of 2 bar, for 120 minutes with a final drying of 30 minutes. Thus one obtains a coating that represents about 5% by weight of the weight of each microbead. The product thus coated has a neutral taste and is suitable for oral administration without significant modification of its rate of liberation in the stomach.

EXAMPLE 7 **Coating solution**

Using a coating solution having the following formulation:

Eudragit L 100	7.3% by weight
Dibutyl phthalate	1.5% by weight
Talc	1.8% by weight
Isopropanol	89.4% by weight

an enteral coating is obtained for the microbeads of Example 2, the coating representing 5 to 10% by weight with respect to the weight of the said microbeads.

EXAMPLES 8-12

By proceeding according to the mode of operation described in Example 1 and varying only the frequency of the vibrations, one obtains microbeads of paracetamol having a diameter of 1.5 mm, 1.0 mm, 0.7 mm, 0.5 mm and 0.1 mm, respectively, with vibrations of 50 Hz, 500 Hz, 1000 Hz, 2000 Hz and 10,000 Hz, respectively.

EXAMPLES 13-14 **Flerobuterol microbeads**

Starting from the following formulations:

	Example 13	Example 14
Flerobuterol	3 g	3 g
Lactose	25 g	-
Beta-cyclodextrin	-	30 g
Dextran 70	25 g	25 g
Sodium saccharinate	3 g	3 g
Water	100 g	100 g

microbeads are prepared according to the invention.

Die diameter: 0.2 mm
Microbead diameter: 0.5 mm

EXAMPLE 15 **Carbinoxamine microbeads**

Starting from the following formulation:

Carbinoxamine maleate	20 g
Glycine	20 g
Dextran 70	10 g
Aspartame	5 g
Xanthan gum	1 g
Water	100 g

microbeads are prepared according to the invention.

Die diameter: 0.2 mm
Microbead diameter: 0.5 mm

EXAMPLES 16-17 **Modafinil microbeads**

Starting from the following formulations:

	Example 16	Example 17
Modafinil*	100 g	100 g
Sodium saccharinate	2 g	2 g
Dextran 70	10 g	20 g
Tween 80	2 g	2 g
hydroxypropyl-ß-cyclodextrin	100 g	-
Lactose or mannitol	-	40 g
Xanthan gum	1 g	1 g
Water	200 g	200 g

(*) Modafinil particle size: 2-5 μm.

Microbeads according to the invention are prepared.
Die diameter: 0.5 mm
Microbead diameter: 1 mm

EXAMPLES 18-19 **Microbeads of dexfenfluramine**

Starting from the following formulations

	Example 18	Example 19
Dexfenfluramine*	300 g	300 g
Dextran 70	20 g	20 g
Xanthan gum	0.5 g	0.5 g
Citric acid	5 g	5 g
Aspartame	6 g	6 g
Mannitol	50 g	-
Beta-cyclodextrin	-	50 g
Water	300 g	300 g

Note
(*) Particle size of the dexfenfluramine: 5-10 μm,
microbeads according to the invention are prepared.
Die diameter: 0.5 mm
Microbead diameter: 1.2 mm

EXAMPLE 20 **Microbeads of loperamide**

Starting from the following formulation:

Loperamide	2 g
Aspartame	20 g
Dextran 70	20 g
Tween 60	1 g
Xanthan gum	1 g
Mannitol	20 g
Water	100 g

microbeads according to the invention are prepared.

Die diameter: 0.5 mm
Microbead diameter: 1 mm

EXAMPLE 21 **Microbeads of lorazepam**

Starting from the following formulation

Lorazepam	2.5 g
Aspartame	8 g
Polyvinylpyrrolidone	25 g
Tween 60	1 g
Xanthan gum	1 g
Dimethyl-ß-cyclodextrin	40 g
Water	100 g

microbeads according to the invention are prepared.

Die diameter: 0.2 mm
Microbead diameter: 0.5 mm.

PATENT CLAIMS

1. Method for the preparation of particles which are useful specifically in therapy, each particle comprising an excipient which forms a matrix and at least one active ingredient that is homogeneously distributed in the bulk of the matrix, the said method being characterized by the fact that it comprises the production of dry cores of regular shape, preferably spherical shape, by extrusion or forming, followed by lyophilization, and then each dry core can be coated, on the one hand, or used in a more complex preparation, on the other hand.

2. Method according to Claim 1, characterized by the fact that it includes
   - preparation of a pasty mixture having a viscosity less than 1 Pa·s, measured at ambient temperature (15-20°C),
   - extrusion of the said pasty mixture and cutting of the extrudate thus obtained, in the form of wet particles with a size generally between 0.01 and 5 mm,
   - solidification of the said particles by contact with an inert fluid at a temperature below 0°C, and
   - drying the said particles thus solidified by cryodesiccation.

3. Method according to Claim 2, characterized by the fact that the solidification is carried out while the wet particles drop in a cooled gaseous fluid that circulates countercurrent to them.

4. Method according to Claim 1, for the preparation of particles, each comprising an excipient, forming a matrix and at least one active ingredient homogeneously distributed in the bulk of the said matrix, the said process, which comprises extrusion operations followed by lyophilization, being characterized by the fact that it comprises the steps consisting of:

(1) preparation of a homogeneous mixture from
   (a) at least one active ingredient,
   (b) a physiologically acceptable hydrophilic excipient, and
   (c) water,

so as to obtain a pasty mixture which has a viscosity less than 1 Pa·s measured at ambient temperature (15-20°C);

(2) extrusion of the homogeneous mixture thus obtained and cutting of the extrudate to obtain wet particles;

(3) solidification of the said particles thus obtained while they fall by gravity in an inert gas flow having a temperature less than 0°C; and

(4) drying the said particles by cryodesiccation.

5. Method according to Claim 4, characterized by the fact that the extrusion is carried out at ambient temperature (15-20°C).

6. Method according to Claim 4, characterized by the fact that the pasty mixture containing water has a viscosity between 0.1 and 0.3 Pa·s at 15-20°C.

7. Method according to Claim 4, characterized by the fact that the hydrophilic excipient (b) contains two essential components:

(b1) a polymeric component which has a molecular weight greater than or equal to 10,000 daltons, swells in the presence of water, and

(b2) a water-soluble or water-dispersible component serving as diluent.

8. Method according to Claim 7, characterized by the fact that component (b1) is a substance chosen from a group comprising gum arabic, xanthan gum, tragacanth gum, alginates, pectinates, polyvinylpyrrolidone, polyethylene glycols, cellulose, carboxymethylcellulose, cellulose ethers, carboxymethylchitin, dextran, chitosan, gelatin, acrylic and methacrylic polymers and copolymers, colloidal silica and their mixtures.

9. Method according to Claim 7, characterized by the fact that component (b2) is a substance chosen from a group consisting of sugars and dextrins.

10. Method according to Claim 7, characterized by the fact that component (b2) is chosen from a group comprising lactose, glycine, mannitol, glucose, sucrose, maltodextrin, cyclodextrin and its derivatives, synthetic sweeteners, natural or synthetic aromas and their mixtures.

11. Method according to Claim 4, characterized by the fact that in step (1) one uses

(a) 100 parts by weight of an active ingredient,

(b1) 10 to 350 parts by weight of a polymer that swells in water, and

(b2) 5 to 350 parts by weight of a substance chosen from sugars, dextrins and their mixtures.

12. Method according to Claim 4, characterized by the fact that in step (1), one also uses

(b3) a surfactant component, specifically at a rate of 0.05 to 3 parts by weight of the said surfactant component per 100 parts by weight of active ingredient.

13. Method according to Claim 4, characterized by the fact that the solidification in step (3) is initiated by the said inert gas current circulating countercurrent to the trajectory of the wet particles then continued to a temperature in the range from -18 to -80°C (preferably -30 to -50°C) in a lyophilizer.

14. Method according to Claim 4, characterized by the fact that it also comprises, after step (4), a step consisting of:

(5) coating each of the lyophilized particles thus obtained, inside a polymer membrane with continuous wall.

15. Method according to Claim 4, characterized by the fact that it comprises the steps consisting of

(1) preparation of a homogeneous mixture at ambient temperature having a viscosity between 0.1 and 0.3 Pa·s from

(a) 100 parts by weight of an active ingredient,

(b) a substantially hydrophilic excipient containing

(b1) 10 to 350 parts by weight of a polymer component having a molecular weight greater than or equal to 10,000 daltons, which swells in water and is chosen from a group comprising gum arabic, xanthan gum, polyvinylpyrrolidone, carboxymethylcellulose, cellulose ethers, dextran and their mixtures,

(b2) 5 to 350 parts by weight of a water-soluble or water-dispersible component serving as diluent, chosen from the group consisting of

lactose, glycine, mannitol, glucose, sucrose, maltodextrin, cyclodextrin, and its derivatives, natural or synthetic aromas and their mixtures, and

(b3) optionally, 0.005 to 3 parts by weight of a surfactant component, and

(c) water in a quantity which is sufficient to obtain the said viscosity of 0.1-0.3 Pa·s;

(2) extrusion of the mixture thus obtained, at ambient temperature (15-20°C) and fragmentation of the extrudate in the form of droplets using vibrations at a frequency of 50 to 10,000 Hz;

(3) solidification of the droplets thus obtained, using an inert gaseous flow in countercurrent, while the said droplets fall by gravity, the solidification being pursued in a lyophilizer up to a temperature of -30°C to -50°C; and

(4) elimination of the water in the said lyophilizer by sublimation.

16. Extruded and lyophilized particle, characterized by the fact that it is obtained according to the method of any of Claims 1 to 15.

17. Particle according to Claim 16, characterized by the fact that it contains

(a) 100 parts by weight of an active ingredient, and

(b) a substantially hydrophilic excipient which contains

(b1) 10 to 350 parts by weight of a polymer component having a molecular weight greater than or equal to 10,000 daltons, which swells in water and is chosen from the group consisting of gum arabic, xanthan gum, polyvinylpyrrolidone, carboxymethylcellulose, cellulose ethers, dextran and their mixtures,

(b2) 5 to 350 parts by weight of a water-soluble or water-dispersible component which serves as diluent and is chosen from the group consisting of lactose, glycine, mannitol, glucose, sucrose, maltodextrin, cyclodextrin and its derivatives, synthetic sweeteners, natural or synthetic aromas and their mixtures, and

(b3) optionally, 0.05 to 3 parts by weight of a surfactant component, and their mixtures,

and by the fact that it is in the form of a microbead having a diameter of 0.05 to 3 mm.

18. Particle according to Claim 16, characterized by the fact that it was coated according to the method of Claim 14, the said particle under consideration together with its coating, constituting an osmotic reservoir.

19. Particle according to Claim 16, characterized by the fact that the active ingredient that it contains is chosen from the group consisting of paracetamol, probucol, piroxicam, phloroglucinol, tiadenol, flerobuterol, modafinil, dexfenfluoramine, carbinoxamine maleate, loperamide, lorazepam, and their mixtures.